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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 10/584,447      | 07/09/2007  | Tomoaki Takakura     | 0032-0291PUS1       | 4157             |

2292 7590 08/05/2011  
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FALLS CHURCH, VA 22040-0747

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| EXAMINER |
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EPPS -SMITH, JANET L

|          |              |
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| ART UNIT | PAPER NUMBER |
|----------|--------------|

1633

|                   |               |
|-------------------|---------------|
| NOTIFICATION DATE | DELIVERY MODE |
|-------------------|---------------|

08/05/2011

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

|                              |                        |                     |  |
|------------------------------|------------------------|---------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b> | <b>Applicant(s)</b> |  |
|                              | 10/584,447             | TAKAKURA ET AL.     |  |
|                              | <b>Examiner</b>        | <b>Art Unit</b>     |  |
|                              | JANET L. EPPS -SMITH   | 1633                |  |

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 20 December 2010.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-10 and 12 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-10 and 12 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 02 June 2010 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/19/2010 has been entered.
2. Claims 1-10, and 12 are presently pending for examination.

### ***Claim Rejections - 35 USC § 112***

3. The rejection of claims 1-15 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in response to Applicant's amendment.
4. The rejection of claim 16 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in response to Applicant's cancellation of this claim.

### ***Claim Rejections - 35 USC § 102***

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

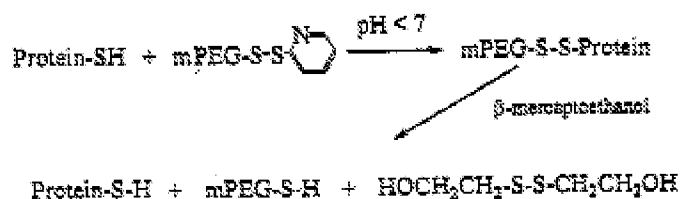
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Art Unit: 1633

6. Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by El Tayar et al. (WO99/55377).

7. El Tayar et al. discloses the following method for the preparation of proteins conjugated to PEG, and method for cleaving the PEG-protein linkage, see page 9 of this reference:

A typical reaction scheme for the preparation of the conjugates of the invention is presented below:



The second line of the above scheme reports a method 15 for cleaving the PEG-protein linkage. The mPEG-SPSS derivative is highly selective for free sulphhydryl groups and reacts rapidly under acidic pH conditions where the IPN- $\beta$  is stable.

### ***Claim Rejections - 35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. Claims 1-10 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over El Tayar et al. as applied above in view of Tan et al. (WO/9640284A1).

Art Unit: 1633

10. The teachings of El Tayar et al. as set forth above are incorporated here.

However, El Tayar et al. does not teach the synthesis of polymer conjugates of methioninase.

11. Tan et al. at page 3, provides a brief description of the invention:

It has now been discovered that methioninase, either in PEGylated form or as produced and purified as a highly pure, endotoxin free recombinant form, can deplete levels of methionine in mammals without harm, can be effectively used to selectively inhibit tumor growth and further can be used to selectively arrest and thereby synchronize tumor cells for antimitotic chemotherapy.

Tan et al. further discloses the following: A chemically modified methioninase comprising methioninase conjugated to a polymer, wherein the polymer is polyethylene glycol. Furthermore, Tan et al. discloses a method of treating a patient having a tumor comprising the step of administering to said patient a therapeutically effective amount of the methioninase-polymer composition.

Page 33 discloses:

Methioninase may be conjugated to a polymer with the purpose of extending its half-life and decreasing its immunogenicity or antigenicity.

Tan et al. does not disclose a reversible process for the conjugation of PEG to methioninase. Additionally, the cited references do not disclose wherein the average 0.7 to 1.3 molecules of a polymer are eliminated per 1 subunit of a protein.

Art Unit: 1633

12. It would have been obvious to the ordinary skilled artisan to apply the methods of polymer conjugation to proteins as described by El Tayar et al. to the design of a methioninase-polymer composition as described by Tan et al. One of ordinary skill in the art would have recognized that the teachings of El Tayar et al. for polymer conjugation would have been readily applicable to any protein that comprises a mercapto group (e.g. cysteine residue), see Figure 8 of Tan et al. Furthermore, the teachings of Tan et al. provide sufficient motivation for the synthesis of PEG conjugated methioninase. Tan et al. teaches that polymer conjugation reduces the antigenicity of the modified protein. One of ordinary skill in the art seeking to restore the antigenicity of a polymer modified protein would have been motivated to use the reversible process described by El Tayar et al.

13. Regarding the average molecules of polymer eliminated per 1 subunit of a protein, since the method of reversing polymer conjugation is disclosed by El Tayar et al. it would have been obvious to the ordinary skill artisan to identify workable ranges by routine experimentation. See MPEP 2144.05.

Art Unit: 1633

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to JANET L. EPPS -SMITH whose telephone number is (571)272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

15. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Smith/  
Primary Examiner, Art Unit 1633